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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,235	10/20/2003	Apostolos Dermatakis	21269US1	4073

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,235	DERMATAKIS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11-14,20 and 21* is/are allowed.

6)☒ Claim(s) *1-10 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04 2/04 2/04 4/04* #6/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. This action is in response to an application filed on 10/20/03. There are twenty-one claims pending and twenty-one under consideration. Claims 1-14, 20, and 21 are compound claims. Claim 15 is a composition claim. Claims 16-19 are method of using claims. This is the first action on the merits. The application concerns some 4-methyl-2-oxo-pyrimido[4,5-d]pyrimidine compounds, compositions, and uses thereof.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for breast, lung, colon, and prostrate cancer, does not reasonably provide enablement for cancer generally. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final sentence on page 246 "[a]lthough many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Determining if any particular cancer would be treatable with Applicants' compounds would require clinical trials in each disease with each compound or to testing them in an assay known to be correlated to clinical efficacy of such treatment. Considering the hundreds of thousands of compounds covered by formula I and the multitude of different cancers, this is a very large degree of

experimentation. b) The direction concerning cancer treatment generally is found in paragraph [0013], page 5. this passage concerns treatment of solid tumors only, not all cancers. Applicants' four *in vitro* assays, concerning the KDR, FGFR, EGFR, and PDGFR enzymes, is described in the passage spanning paragraph [0177], page 70 to paragraph [0184], page 73. There is qualitative data on seventeen compounds. Applicants' *in vitro* assay, concerning the [Brdu] test, is described in the passage spanning paragraph [0185], page 73 to paragraph [0186], page 76. There is qualitative data on twelve compounds. Applicants describe formulations in the passage spanning paragraph [0074], page 19 to paragraph [0077], page 21 and in pages 76-79. The experiments described on pages 76-79 appear to be merely prophetic. The doses required to practice their invention are taught in the passage spanning paragraph [0078], page 20 to paragraph [0080], page 21. A 1,000-fold range of doses is proposed. c) There is no working example of cancer treatment in man or animal in the specification. There is no working example of any dosage or dosing schedule required to practice the invention. d) The claims rejected are drawn to clinical medicine and are therefore physiological in nature.

e) The state of the art in cancer therapy is the remarkable advances in chemotherapy have seen the development of specific compounds to treat specific

types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The state of the art in cancer therapy using protein kinase inhibitors is provided by Noble (Science) who states in the first two paragraphs, third column, page 1800 that investigational use for the treatment of two cancers, lung and pancreatic, was under way in 2004. The state of the art in cancer therapy using EGFR inhibitors is provided by Anderson (Expert Opin. Investig. Drugs), who states in the second and third paragraph on page 581 that ZD1839 and OSI-774, two such inhibitors treat colon, lung, and head and neck tumors. Laird (Expert opin. Investig. Drugs) states in Tbale 2, page 55 that lung and pancreatic caners are targets of the EGFR inhibitors , ZD1839 (Iressa) and OSI-774 (Tarceva). In the final pargarph on page 60 the utility of such inhibitiors for treating "a limited number of malignancies" is stated. Traxler (Expert Opin. Ther. Targets) states on page 216 in Table 1 that breast, lung, prostrate, colon, and glioma tumors are the targets of such inhibitors. In the paragrph spanning pages 227 to 228, clinical failures with such ibhinitors are discussed, which emphasisizes the lack of prdictability in this art.

f) The artisan using Applicants invention would be a Board Certified physician in oncology with an MD degree and several years of experience. g) It is

well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The intractability of cancers generally is clear evidence that the skill level in this art is low relative to the difficulty of the task. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of diseases embraced by claim 6. Thus, the scope of the claims is broad.

Applicants' critical failure is the lack of a single specific cancer they intend to treat and the complete lack of data showing efficacy of their compounds against that cancer. Cancer is just an umbrella term. It includes solid tumors as wells as leukemia. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. The present specification says, in effect: here are the compounds and how to make them. You figure out what cancers they might be useful against. This is not the "immediate benefit to the public" required by *Cross et al. v. Iizuka et al* 224 USPQ 739, and *Nelson v. Bowler* 206 USPQ 881.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

3.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January

1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 and 15-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 16-20 of copending Application No. 10/689,438. Although the conflicting claims are not identical, they are not patentably distinct from each other because except for the negative proviso at the end of claim 1 of copending Application No. 10/689,438, these claims use the same formula and are of the same scope. In the present case, Examples 21b-21g have R^3 = fluorine and provide the guidance to pick the variables needed to arrive at the claims of copending Application No. 10/689,438.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

5. Claims 11-14, 20, and 21 are allowed.

Conclusion

6. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private

PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

7. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Primary Examiner
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TCMcK/me